7/29/15 Science Board Meeting - Open Public Hearing – Written Submission

Dear Mr. Raghuwanshi:

In connection with the meeting of the FDA Science Advisory Board, you should make the board aware of recent developments in connection with use of antisense oligonucleotides for microbial resistant infection and pandemic influenza. Given the recent outbreaks of Ebola, and the continuing spread of MERS-CoV, development of new approaches for precision medicines which interfere with viral reproduction or therapeutic use for resistant microbes should be given a high priority by the FDA, BARDA, and the Dept of Defense Labs such as NMRC and USAMRIID.

See, for example, the publication expected in the New England Journal of Medicine for July 23. Therapeutics which can interfere with infections and infectious diseases without dose limits resulting from adverse effects are the types of approaches which may enable the United States to build stockpiles and treatment plans for either pandemic or bioterrorism events, or nosocomial infections resulting from such diseases. The Science Advisory Board should be aware of the potential of these targeted biomolecules.

Sarepta Therapeutics Announces New England Journal of Medicine Publication of Phase I Clinical Data of Marburg Drug Candidate, AVI-7288, Supporting Safety of the PMOplus® platform

CAMBRIDGE, Mass.--(BUSINESS WIRE)--

Sarepta Therapeutics, Inc. (SRPT), a developer of innovative RNA-targeted therapeutics, today announced the publication of results from a multiple ascending dose study to determine the safety of AVI-7288, a PMO*plus*® antisense oligonucleotide, in healthy adult volunteers, in the July 23, 2015 issue of The New England Journal of Medicine. The results of the study, conducted in collaboration with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), demonstrated no clinical or toxicologic safety concerns with AVI-7288, an investigational treatment for Marburg Virus (MARV) infection. These results add to the continued documentation of safety data for Sarepta's PMO-based technology.

AVI-7288 utilizes Sarepta's advanced and proprietary PMO*plus*® technology. AVI-7288 is designed to bind to viral messenger RNA encoding Marburg Virus nucleoprotein to inhibit nucleoprotein synthesis and prevent viral replication and assembly. This mechanism of AVI-7288 is fundamentally distinct from other RNA-based anti-infective therapies that utilize a gene editing or degradation pathway. Additionally, this approach highlights the flexibility and precision of the PMO-based platform.

The Phase I clinical study was a randomized, double-blind, placebo-controlled trial designed to characterize the safety, tolerability and pharmacokinetics of AVI-7288 after daily repeat dosing. Over 14 days, 40 healthy human volunteers (8 per dose group) were dosed with up to 16 mg/kg/day, representing the highest continuous dosing of any PMO*plus*® or any other antisense oligonucleotide. This dosing also exceeded the predicted human efficacious dose for AVI-7288 estimated by three different models based upon nonhuman primate studies demonstrating up to 100% animal survival, including in a delayed time to treat setting.

In healthy human volunteers, no significant safety concerns or dose-dependent adverse side effects of AVI-7288 were reported with respect to any safety end point evaluated, nor were any

gross abnormalities in renal function or biomarkers of renal dysfunction observed. The maximum dose of AVI-7288 that could be administered without raising significant safety concerns was not reached.

“These data add to the growing body of evidence underpinning the safety profile of Sarepta’s PMO-based chemistry platform and its potential in treating a variety of diseases.” stated Michael Wong, MD, Senior Medical Director, Infectious Diseases. “We look forward to continuing to build upon these data and further demonstrating the versatility and utility of this novel precision medicine approach in tackling some of the most challenging infectious disease threats today including pandemic influenza and antimicrobial resistance.”

“Results described in this manuscript provide further confirmation that PMO-based antisense therapeutics can protect against a highly pathogenic virus in nonhuman primate disease models and, importantly, that the dose regimen that we predict to be efficacious in humans is not likely to compromise patient safety during treatment,” said Sina Bavari, Ph.D., USAMRIID Science Director.

This work was conducted under contract with the Department of Defense Medical Countermeasures Systems/Joint Product Management Office of BioDefense Therapeutics (BD-Tx).

Kermit R. Kubitz
[redacted]